

CLAIMS

What is claimed is:

1. A composition comprising an isolated polynucleotide encoding a protein having TNF-R1-DD ligand protein activity.
2. The composition of claim 1 wherein said polynucleotide is selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 2 to nucleotide 1231;
 - (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:1;
 - (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2;
 - (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:2; and
 - (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).
3. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 2 to nucleotide 415;
 - (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:3;
 - (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4;
 - (d) a polynucleotide encoding an TNF-R1-DD ligand⁺ protein comprising a fragment of the amino acid sequence of SEQ ID NO:4; and
 - (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

5 4. A composition of claim 1 wherein said polynucleotide is operably linked
to an expression control sequence.

 5. A host cell transformed with a composition of claim 4.

10 6. The host cell of claim 5, wherein said cell is a mammalian cell.

 7. A process for producing an TNF-R1-DD ligand protein, which
comprises:

 (a) growing a culture of the host cell of claim 5 in a suitable culture
15 medium; and

 (b) purifying the TNF-R1-DD ligand protein from the culture.

 8. A composition comprising a protein having TNF-R1-DD ligand protein
activity.

20 9. The composition of claim 8 wherein said protein comprises an amino
acid sequence selected from the group consisting of:

 (a) the amino acid sequence of SEQ ID NO:2; and

 (b) fragments of the amino acid sequence of SEQ ID NO:2;
25 said protein being substantially free from other mammalian proteins.

 10. The composition of claim 8 wherein said protein comprises an amino
acid sequence selected from the group consisting of:

 (a) the amino acid sequence of SEQ ID NO:4; and

30 (b) fragments of the amino acid sequence of SEQ ID NO:4;
said protein being substantially free from other mammalian proteins.

 11. The composition of claim 8 wherein said protein comprises an amino
acid sequence selected from the group consisting of:

35 (a) the amino acid sequence of SEQ ID NO:6; and

 (b) fragments of the amino acid sequence of SEQ ID NO:6;

- 5 (d) fragments of the amino acid sequence of SEQ ID NO:4;
(e) the amino acid sequence of SEQ ID NO:6;
(f) fragments of the amino acid sequence of SEQ ID NO:6;
(g) the amino acid sequence of SEQ ID NO:8; and
(h) fragments of the amino acid sequence of SEQ ID NO:8.

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16. A method of preventing or ameliorating an inflammatory condition which comprises administering a therapeutically effective amount of a composition of claim 12.

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17. TNF-R1-DD ligand protein produced according to the method of claim 7.

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18. A method of inhibiting TNF-R death domain binding comprising administering a therapeutically effective amount of a composition of claim 12.

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19. A method of preventing or ameliorating an inflammatory condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

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20. A method of inhibiting TNF-R death domain binding comprising administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

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21. A composition comprising an inhibitor identified according to the method of claim 14.

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5 22. The composition of claim 21 further comprising a pharmaceutically acceptable carrier.

 23. A method of preventing or ameliorating an inflammatory condition comprising administering to a mammalian subject a therapeutically effective amount
10 of the composition of claim 22.

 24. A method of inhibiting TNF-R death domain binding comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.
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 25. A composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

20 26. A method of identifying an inhibitor of TNF-R death domain binding which comprises:

 (a) transforming a cell with a first polynucleotide encoding an TNF-R death domain protein, a second polynucleotide encoding an TNF-R1-DD ligand protein, and at least one reporter gene, wherein the expression of the reporter gene is regulated by the binding of the TNF-R1-DD ligand protein
25 encoded by the second polynucleotide to the TNF-R death domain protein encoded by the first polynucleotide;

 (b) growing the cell in the presence of and in the absence of a compound; and

30 (c) comparing the degree of expression of the reporter gene in the presence of and in the absence of the compound;

wherein the compound is capable of inhibiting TNF-R death domain binding when a decrease in the degree of expression of the reporter gene occurs.

35 27. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 2 to nucleotide 1231;
- (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:1, which encodes a protein having TNF-R1-DD ligand protein activity;
- 10 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2;
- (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 and having TNF-R1-DD ligand protein activity;
- 15 (e) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 2 to nucleotide 415;
- (f) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:3, which encodes a protein having TNF-R1-DD ligand protein activity;
- 20 (g) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4;
- (h) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 and having TNF-R1-DD ligand protein activity;
- 25 (i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 2 to nucleotide 559;
- (j) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:5, which encodes a protein having TNF-R1-DD ligand protein activity;
- 30 (k) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6;
- (l) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 and having TNF-R1-DD ligand protein activity;
- 35 (m) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 57 to nucleotide 875;

- 5 (n) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:7, which encodes a protein having TNF-R1-DD ligand protein activity;
 - (o) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8;
 - 10 (p) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 and having TNF-R1-DD ligand protein activity; and
 - (q) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(p), which encodes
 - 15 a protein having TNF-R1-DD ligand protein activity.
28. The method of claim 26 wherein the cell is a yeast cell.
29. The composition of claim 1 wherein said polynucleotide sequence is
- 20 selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 2 to nucleotide 931;
- (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:9;
- 25 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10;
- (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:10; and
- (e) a polynucleotide capable of hybridizing under stringent
- 30 conditions to any one of the polynucleotides specified in (a)-(d).
30. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID
- 35 NO:11 from nucleotide 2 to nucleotide 1822;

- 5 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:11;
- (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12;
- (d) a polynucleotide encoding an TNF-R1-DD ligand protein
10 comprising a fragment of the amino acid sequence of SEQ ID NO:12; and
- (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).
31. The composition of claim 8 wherein said protein comprises an amino
15 acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:10; and
- (b) fragments of the amino acid sequence of SEQ ID NO:10;
said protein being substantially free from other mammalian proteins.
- 20 32. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:12; and
- (b) fragments of the amino acid sequence of SEQ ID NO:12;
said protein being substantially free from other mammalian proteins.
- 25 33. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:10;
- (b) fragments of the amino acid sequence of SEQ ID NO:10;
- 30 (c) the amino acid sequence of SEQ ID NO:12; and
- (d) fragments of the amino acid sequence of SEQ ID NO:12.
34. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:
- 35 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 2 to nucleotide 931;

- 5 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:9, which encodes a protein having TNF-R1-DD ligand protein activity;
- (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10;
- 10 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 and having TNF-R1-DD ligand protein activity;
- (e) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 2 to nucleotide 1822;
- 15 (f) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:11, which encodes a protein having TNF-R1-DD ligand protein activity;
- (g) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12; and
- 20 (h) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 and having TNF-R1-DD ligand protein activity; and
- (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), which encodes a protein having TNF-R1-DD ligand protein activity.
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35. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 3 to nucleotide 2846;
- (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:13;
- (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14;
- 35 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:14; and

5 (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

36. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:
10 (a) the amino acid sequence of SEQ ID NO:14; and
(b) fragments of the amino acid sequence of SEQ ID NO:14;
said protein being substantially free from other mammalian proteins.

37. The method of claim 14 wherein said TNF-R1-DD ligand protein
15 comprises an amino acid sequence selected from the group consisting of:
(a) the amino acid sequence of SEQ ID NO:14; and
(b) fragments of the amino acid sequence of SEQ ID NO:14.

38. The method of claim 26 wherein the second polynucleotide is selected
20 from the group consisting of:
(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 3 to nucleotide 2846;
(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:13, which encodes a protein having TNF-R1-DD
25 ligand protein activity;
(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14;
(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 and having TNF-R1-DD ligand protein activity; and
30 (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d), which encodes a protein having TNF-R1-DD ligand protein activity.

39. The composition of claim 1 wherein said polynucleotide sequence is
35 selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 326 to nucleotide 5092;
- (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:15;
- 10 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16;
- (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:16; and
- (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).
- 15 40. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:16; and
- (b) fragments of the amino acid sequence of SEQ ID NO:16;
- 20 said protein being substantially free from other mammalian proteins.
41. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:16; and
- 25 (b) fragments of the amino acid sequence of SEQ ID NO:16.
42. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 326 to nucleotide 5092;
- 30 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:15, which encodes a protein having TNF-R1-DD ligand protein activity;
- (c) a polynucleotide encoding an TNF-R1-DD ligand protein
- 35 comprising the amino acid sequence of SEQ ID NO:16;

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5 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 and having TNF-R1-DD ligand protein activity; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d), which encodes
10 a protein having TNF-R1-DD ligand protein activity.

43. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

15 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 14 to nucleotide 2404;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:17;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18;

20 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:18; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

25 44. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18; and

(b) fragments of the amino acid sequence of SEQ ID NO:18;
said protein being substantially free from other mammalian proteins.

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45. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18; and

(b) fragments of the amino acid sequence of SEQ ID NO:18.

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5 46. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 14 to nucleotide 2404;

10 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:17, which encodes a protein having TNF-R1-DD ligand protein activity;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18;

15 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 and having TNF-R1-DD ligand protein activity; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d), which encodes a protein having TNF-R1-DD ligand protein activity.